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## **The cellular orchestra in skin allergy; are differences to lung and nose relevant?**

Akdis, Mübeccel

**Abstract:** PURPOSE OF REVIEW: It has been a long lasting question that although a similar peripheral allergen-specific immune response has been observed, why some patients show only atopic dermatitis, rhinitis and asthma alone or their combinations. The answer resides in the propensity of resident tissue cells and local antigen-presenting cells and T cells for developing an allergic inflammatory immune response. Antigen-presenting cells introduce processed allergens to T helper lymphocytes, where a decision of developing different types of T cell immunity is given under the influence of several cytokines, chemokines, costimulatory signals and regulatory T cells. RECENT FINDINGS: We focused in this review article on effector T cell subsets, which have been recently described such as Th9, Th17 cells and Th22 cells, which are characterized by their IL-9 and IL-10, IL-17 (or IL-17A) and IL-22 expression, respectively together with other proinflammatory cytokines, which coordinate local tissue inflammation. Both naturally occurring CD4+CD25+ regulatory T (Treg) cells and inducible populations of allergen-specific, IL-10-secreting Treg type 1 cells inhibit allergen-specific effector cells and have been shown to play a central role in the maintenance of peripheral homeostasis and the establishment of controlled immune responses in allergic inflammatory tissues. SUMMARY: Better understanding and characterization of newly described effector cell subsets and their interaction between antigen presenting cells and resident tissue cells will enlighten our knowledge on the mechanisms of allergic diseases.

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# The cellular orchestra in skin allergy: are differences to lung and nose relevant?

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## Purpose of review

It has been a long lasting question that although a similar peripheral allergen-specific immune response has been observed, why do some patients show only atopic dermatitis, rhinitis and asthma alone or their combinations? The answer resides in the propensity of resident tissue cells and local antigen-presenting cells and T cells for developing an allergic inflammatory immune response. Antigen-presenting cells introduce processed allergens to T helper lymphocytes, where a decision of developing different types of T cell immunity is given under the influence of several cytokines, chemokines, costimulatory signals and regulatory T cells.

## Recent findings

We focused in this review article on effector T cell subsets, which have been recently described such as Th9, Th17 cells and Th22 cells, which are characterized by their IL-9 and IL-10, IL-17 (or IL-17A) and IL-22 expression, respectively together with other proinflammatory cytokines, which coordinate local tissue inflammation. Both naturally occurring CD4<sup>+</sup>CD25<sup>+</sup> regulatory T (Treg) cells and inducible populations of allergen-specific, IL-10-secreting Treg type 1 cells inhibit allergen-specific effector cells and have been shown to play a central role in the maintenance of peripheral homeostasis and the establishment of controlled immune responses in allergic inflammatory tissues.

## Summary

Better understanding and characterization of newly described effector cell subsets and their interaction between antigen presenting cells and resident tissue cells will enlighten our knowledge on the mechanisms of allergic diseases.

## Keywords

allergy, antigen presentation, atopic dermatitis, immunoregulation, skin, T cell response and T cell subsets

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## Introduction

Major causative factors added to the genetic propensity of developing IgE antibodies responsible for symptoms and signs of allergic disorders [1] can be listed as encounter with various new molecules in air, water and diet, and living in a more polluted world with less exposure to infections and infectious agents. Clinical manifestations are allergic rhinitis, allergic asthma, food allergy, allergic skin inflammation, ocular allergy, as single or combined disease [2]. Biochemical properties of the allergen, stimulating factors of the innate immune response around the allergen substances at the time of exposure, stability of the allergen in the tissues, digestive system, skin or mucosa, and the dose and time of stay in lymphatic organs during the interaction with the immune system are all possible confounding factors causing an antigen to become an allergen [2]. Antigen specificity in an evolved response of both T and B-lymphocytes takes part in

adaptive immune response. T lymphocytes are responsible for cell-mediated immune responses, where B-lymphocytes are for humoral immune responses [3]. Two essential factors of adaptive immunity are specificity and memory, which is determined by the existing frequency of circulating T and B cells and readiness to respond to antigens.

Dendritic cells are complex cell populations that differ in their anatomic location, antigen recognition, processing machinery, and migratory capacity. Dendritic cells stay as sentinels that take up exogenous antigens and transmit the information into the immune system by migrating to draining lymph nodes, and presenting the processed antigens to T cells resulting in T-cell differentiation and activation [4,5]. Content of micromillieu and several cytokines and other cofactors released from dendritic cells are essential for the differentiation of naive T cells into T helper (Th)1, Th2, Th9, Th17 and Th22 effector

T cell subsets [6]. Expansion of allergen-specific Th2 cells results in production of IL-4 and IL-13, which induce immunoglobulin class switching to IgE and clonal expansion of naive and IgE<sup>+</sup> memory B-cell populations. When IgE bound to FcεRI (high-affinity receptor for IgE) on mast cells and basophils crosslinks with the specific allergen, release of vasoactive amines (such as histamine), lipid mediators, chemokines and cytokines occur, which are responsible for the signs and symptoms of immediate phase of the allergic reactions [7]. This mast cell or basophil degranulation should be very important for the development of further Th2 responses because basophil IL-4 has been shown to be essential in their differentiation [8,9<sup>\*</sup>].

Atopic dermatitis (AD) patients possess increased numbers of activated cutaneous lymphocyte-associated antigen (CLA)-bearing T cells in the circulation and increased levels of serum L-selectin, a marker for leukocyte activation correlating with atopic dermatitis disease severity [10–12]. CLA defines a subset of circulating memory T cells that selectively localizes to cutaneous sites. CLA<sup>+</sup> T cells constitute only 10–15% of the circulating T-cell pool and do not exceed 5% of lymphocytes within noncutaneous inflamed sites [13]. CLA is expressed on Th1 cells during the differentiation process and can be induced on Th2 cells by stimulation with bacterial superantigen and/or IL-12 [14,15]. Improvement in eczematous skin lesions seen in primary T-cell immunodeficiency disorders after successful bone marrow transplantation also remarks for the key role of immune effector T cells in atopic dermatitis. Dermal cellular infiltrate in atopic dermatitis mainly consists of CD4<sup>+</sup> and CD8<sup>+</sup> T cells with a CD4/CD8 ratio similar to peripheral blood levels [16,17]. In studies [16,17], CD8<sup>+</sup>CLA<sup>+</sup> T cells were demonstrated to be as potent as CD4<sup>+</sup>CLA<sup>+</sup> T cells in induction of IgE and inhibition of eosinophil survival.

The role of aeroallergens in T cell activation in atopic dermatitis has been extensively studied [18,19]. Aeroallergens can induce both immediate type and delayed type responses in the skin [19]. The frequency of aeroallergen-specific T cells was found to be less than 1% in nonchallenged atopic dermatitis lesions [20]. In addition, such allergen-specific T cells can be detected in the skin of atopic patients after allergen administration, without any signs of atopic dermatitis lesions [21]. The contribution of food allergens in the exacerbation of atopic dermatitis by T cell activation was also demonstrated [22]. It has recently been demonstrated that allergens such as house dust mite (*Dermatophagoides pteronyssinus*) and birch pollen induce atopy patch test reactivity in NAD patients with the presence of specific IgG, but not IgE antibodies [23]. Normally allergen-specific T cell responses in food and aeroallergen allergy are confined to

CD4<sup>+</sup> T cells. This, however, may not explain the activation and recruitment of CD8<sup>+</sup> T cells in atopic dermatitis skin lesions. It is also known that bacterial superantigens can interact with certain Vβ elements of the T cell receptor (TCR) leading to activation, expansion, anergy or deletion of T cells. It is evident from mouse studies that superantigen response of T cells is not restricted to CD4<sup>+</sup> T cells. CD8<sup>+</sup> T cells [24] and even CD4<sup>−</sup> CD8<sup>−</sup> T cells can respond to superantigenic stimuli [25]. This may explain the existence and activation of CD8<sup>+</sup> T cells in eczema lesions and their contribution to IgE production and eosinophil survival and development, chronicity and exacerbation of atopic dermatitis [16,17]. One of the factors that may contribute to the pathophysiology of atopic dermatitis is autoreactivity to human proteins [26,27]. IgE against autoantigens can stimulate type 1 hypersensitivity reactions and dendritic cells, and induce the proliferation of autoreactive T cells [28]. Another widely supported view is that dermal dendritic cells and epidermal Langerhans cells display an abnormal hyperstimulatory function for T cells, in addition to IL-12 and IL-18 production. IgE FcεRI and FcεRII (CD23) are upregulated in CD1a positive cells in atopic dermatitis. CD1a is a marker of dermal dendritic cells and Langerhans cells [29].

### Allergen recognition by the immune system

Dendritic cells play roles in the induction of protective T cell immunity, as well as in tolerance induction. The two distinct dendritic cell subsets that have been recognized in humans are myeloid dendritic cells (mDCs) and plasmacytoid dendritic cells (pDCs) [30]. Myeloid dendritic cells express TLR2–TLR6 and TLR8 and can produce IL-12 in response to the bacterial and viral stimuli, whereas pDCs express TLR7 and TLR9 and have the ability to produce large amounts of type 1 interferons in antiviral immune responses [31–34]. It has been suggested that pDCs directly suppress the potential of mDCs to generate effector T cells [35]. It was reported that pDCs could stimulate the formation of Treg cells, possibly in an ICOS-L-dependent way [32,35]. Depletion of pDCs from the lungs has abolished tolerance to inhaled antigens [35,36]. On the contrary, the two distinct dendritic cell populations that have been identified in inflamed epidermis of atopic dermatitis are the classical Langerhans cells and the inflammatory dendritic epidermal cells (IDEC) [37]. IDEC population clearly induces a Th1 profile, whereas Langerhans cell population rather induces a Th2 type of T-cell response [38]. Concerning dendritic cells and Langerhans cells, the expression of IgE FcεRI and its increase on the surface of these cells is strongly related to distinct type of inflammatory status [39].

Tissue-resident mast cells are important in allergic diseases. In a mouse model of allergic airways inflammation,

an increase in peribronchiolar mast cells was associated with increased concentrations of the chemokine CCL2 in the lungs. Mast cell progenitors (MCps) arising in bone marrow are recruited to tissues by transendothelial migration, and CCL2 was chemotactic for MCps, suggesting a complex role of the CCL2/CCR2 axis in recruiting MCps during pulmonary inflammation [40<sup>\*</sup>]. Recently, it was shown that Znt5 is selectively required for the mast cell-mediated delayed-type allergic response, and Zinc (Zn) is a novel player in mast cell activation [41<sup>\*</sup>].

Recent research has substantially expanded our view on the function of natural killer (NK) cells in the immune system. In patients with allergic diseases, the production of Th2 cytokines by NK cells contributes to the known immune deviation [42,43]. It was also shown that NK cells affect skin immune responses to haptens by releasing type 1 cytokines and inducing keratinocyte apoptosis. More than 90% of NK cells isolated from allergic contact dermatitis skin showed a CD3<sup>+</sup>CD56<sup>+</sup> (high) CD16<sup>+</sup> phenotype. Skin NK lymphocytes displayed a CXCR3<sup>+</sup>CCR6<sup>+</sup>CDR5<sup>+</sup> chemokine receptor asset for homing into inflamed skin, but not CD62L and CCR7 for lymph node homing. Those findings underline the importance

of the interaction between innate and adaptive immune mechanisms for amplification of skin allergic responses to haptens and full expression of allergic contact dermatitis [44].

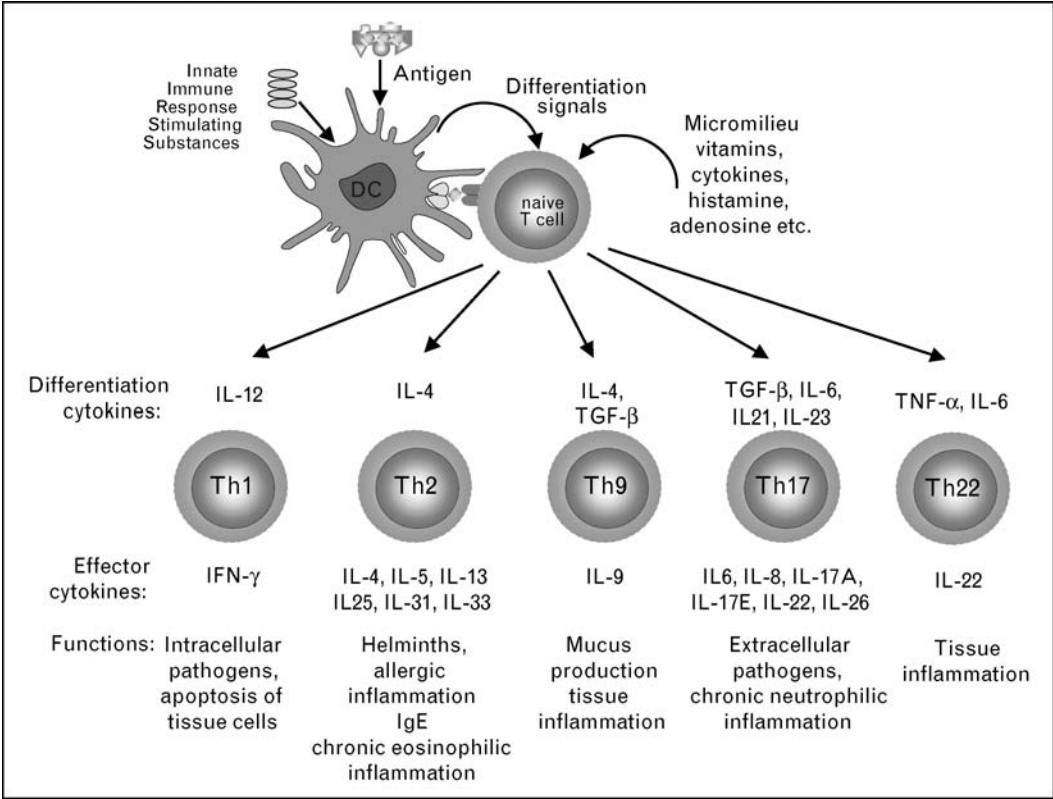
### Effector T cell subsets

Activated effector T cells play an essential role in allergy and asthma and other inflammatory diseases (Fig. 1).

### Th1 and Th2 cells

Formerly, subsets of CD4<sup>+</sup> Th lymphocytes were categorized as Th1 and Th2 based on their distinct cellular functions and cytokine secretion capacities [45]. Our knowledge of the pathogenesis of atopic diseases has broadened to incorporate the contribution of Treg cells and the newly described proinflammatory Th9, Th17, and Th22 cell lineages. The commitment of peripheral T-cell clones to undergo differentiation into one of those lineages is controlled by key transcriptional regulators: T-box expressed in T cells (Th1), GATA-3 (Th2), fork-head box p3 (FOXP3, Treg cells), retinoid-related orphan receptor  $\gamma$ /retinoid-related orphan receptor  $\alpha$  (Th17)

**Figure 1** Differentiation of effector T cells depending of the adjuvanticity of the substances coexposed with the antigen and status of the cells and cytokines in the microenvironment – naïve T cells can differentiate into Th1, Th2, Th9, Th17, and Th22 types of cells



On the basis of their respective cytokine profiles, responses to chemokines and interactions with other cells, these T-cell subsets can promote different types of inflammatory responses.

and ETS family member PU.1 (Th9) [46,47\*\*]. Counter-regulation between these effector subsets has been continuously proposed [48–51]. The activation of T-bet as a key transcription factor of Th1 cells inhibits both Th2 cell-mediated eosinophil recruitment and Th17 cell-mediated neutrophil recruitment into the airways [52]. An association between a specific T-bet haplotype and allergic asthma in children is demonstrated [53].

Predominant Th2 profile in atopic diseases might be a result of the increased tendency to activation and apoptosis of high IFN- $\gamma$ -producing Th1 cells [54]. Th1 cells, particularly their high IFN- $\gamma$ -producing fraction, and CXCR3<sup>+</sup> T cells showed significantly increased apoptosis in atopic individuals [54]. Th1 cells are implicated in cell-mediated defence against intracellular microorganisms and in promotion of memory IgG responses and are characterized by IL-2, interferon (IFN)- $\gamma$  and TNF- $\beta$  cytokine profiles. These cells can efficiently contribute to the effector phases in allergic diseases by exerting their roles in apoptosis of the epithelium in asthma and atopic dermatitis [55,56]. It was shown that dysregulated apoptosis in skin-homing T cells and keratinocytes contributes to the elicitation and progress of atopic dermatitis. T cell survival is enhanced in the skin by cytokines and extracellular-matrix proteins [57]. These activated T cells induce keratinocyte apoptosis, leading to eczema formation [58]. A new study [59\*\*] demonstrated that IL-32 as a new cytokine is expressed by human primary keratinocytes and modulates keratinocyte apoptosis and might also play a role in the formation and maintenance of atopic dermatitis lesions. IL-27 has been described to support T cell-polarization along the Th1 lineage but also to exert important anti-inflammatory responses in later phases of inflammation in murine models. IL-27 also acts as a priming signal on keratinocytes able to amplify chemokine production and surface molecule expression when used before a second signal, such as TNF- $\alpha$ . The effect of IL-27 could not be mimicked by IL-6, IL-12 or IL-23 and IL-27 might act in an inflammatory, disease-maintaining manner in the epidermal compartment of patients with eczema [60\*\*].

Th2 cells engage in immunity to parasites, secrete IL-4, IL-5 and IL-13 and predominantly mediate IgE responses, eosinophilia and allergic inflammation [7,61]. IL-4 plays an important role in regulating epidermal homeostasis and innate barrier function [62]. It has been shown that OX40 ligation upregulates IL-4 production which promotes Th2 polarization [63]. Thymic stromal lymphopoietin (TSLP) as a novel growth factor is produced by epithelial cells and has master roles at the epithelial cell and dendritic cell interface of allergic inflammation [64]. TSLP has been suggested to activate human mDCs to induce inflammatory Th2 responses [65]. TSLP-induced dendritic cells mature and migrate into the draining lymph nodes to

initiate the adaptive phase of allergic immune response. TSLP-induced dendritic cells express OX40L, which triggers the differentiation of allergen-specific naive CD4<sup>+</sup> T cells to inflammatory Th2 cells [66]. IL-25 (IL-17E), a member of the IL-17 family of immunoregulatory cytokines, has been implicated in the regulation of Th2 type immunity [67]. Blocking IL-25 in an experimental model of allergic asthma prevented AHR and reduced IL-5 and IL-13 production, eosinophil infiltration, goblet cell hyperplasia, and serum IgE secretion [68]. IL-33, a recently discovered cytokine, is a potent inducer of Th2 type responses via its receptor ST2 [69]. In-vitro polarized Th2 cells produce enhanced amounts of Th2 type cytokines in the presence of IL-33. Over-expression of IL-33 leads to spontaneous pulmonary inflammation in mIL-33 transgenic mice [70].

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### Th17 cells

Th17 cells and their prototype cytokines IL-17A coordinate local tissue inflammation through upregulation of proinflammatory cytokines and chemokines [71,72]. Epicutaneous sensitization in the absence of IL-4/IL-13 induces an exaggerated Th17 response systemically and in lungs after antigen challenge that results in airway inflammation and airway hyperresponsiveness [73]. Differentiation of Th17 (IL-17A-producing and IL-17F-producing) cells is induced by IL-1 $\beta$ , IL-6, IL-21, IL-23, and TGF- $\beta$  [6]. IL-17 act as a recruitment and survival factor for macrophages and coordinate granulocyte influx in allergic airway inflammation models [74,75]. Vaccinia virus inoculation in OVA-sensitized skin induced marked local expression of IL-17 transcripts and massive neutrophil infiltration. Treatment with anti-IL-17 decreased the size of primary lesions, numbers of satellite lesions and viral loads. These findings suggest that IL-17 may be a potential therapeutic target in eczema vaccinatum [76]. There are also pharmacological measures to manipulate these Th subsets. Prostaglandin E2 (PGE2) acts on its receptor EP4 on T cells and dendritic cell not only facilitates Th1 cell differentiation but also amplifies IL-23-mediated Th17 cells in regional lymph nodes and suppresses the disease progression in mice subjected to experimental autoimmune encephalomyelitis or contact hypersensitivity. Thus, PGE2-EP4 signaling promotes immune inflammation through Th1 differentiation and Th17 expansion, and EP4 antagonism may be therapeutically useful for various immune diseases [77].

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### Th9 and Th22 cells

More recently, another two subsets of effector CD4<sup>+</sup> Th cells, named Th9 and Th22 cells, have been described, even if their pathophysiological meaning is still unclear. Recent comparative analysis of different subsets of T helper cells for cytokine production revealed that

activation of naive CD4 T cells in the presence of TGF- $\beta$  and IL-4 significantly enhances IL-9 and IL-10 production but not other Th2 cytokines, indicating that IL-9-producing cells are not Th2 cells [78,79] suggesting that they represent a new subset of T helper cells with the transcription factor PU.1 [47<sup>••</sup>]. Functional analysis of Th9 cells has also confirmed that in contrast to Treg cells, Th9 are neither anergic nor suppressive, as they can vigorously proliferate and along with effector T cells they further enhance T-cell proliferation [78]. Studies in allergic patients has revealed that T cells can be a significant source of IL-9 and mouse models have revealed that IL-9 has multiple effects in the development and maintenance of allergic inflammation and airway remodeling. It is as yet unknown whether IL-9-secreting T cells are distinct from Th2 cells or whether Th2 cells can be reprogrammed into Th9 cells during the allergic response *in vivo* [80].

A less well defined tissue-instructing cytokine is IL-22. Recent studies [81,82<sup>••</sup>] have determined that some T cells express IL-22 independently of IL-17, particularly CCR10+ T cells. IL-22 belongs to the IL-10 cytokine family and binds to a heterodimeric receptor consisting of the IL10 receptor (IL-10R)  $\beta$  chain and the IL-22R [83]. The IL-22R is expressed almost exclusively on nonimmune cells, suggesting that IL-22, like IL-17, acts primarily on tissue cells [83]. It is consistently described to enable epithelial innate immune responses, which can be detrimental or protective. In a recent study [84<sup>•</sup>], it was shown that Th22 clones derived from patients with psoriasis were stable in culture and exhibited a transcriptome profile clearly separate from those of Th1, Th2, and Th17 cells; it included genes encoding proteins involved in tissue remodeling and chemokines involved in angiogenesis and fibrosis.

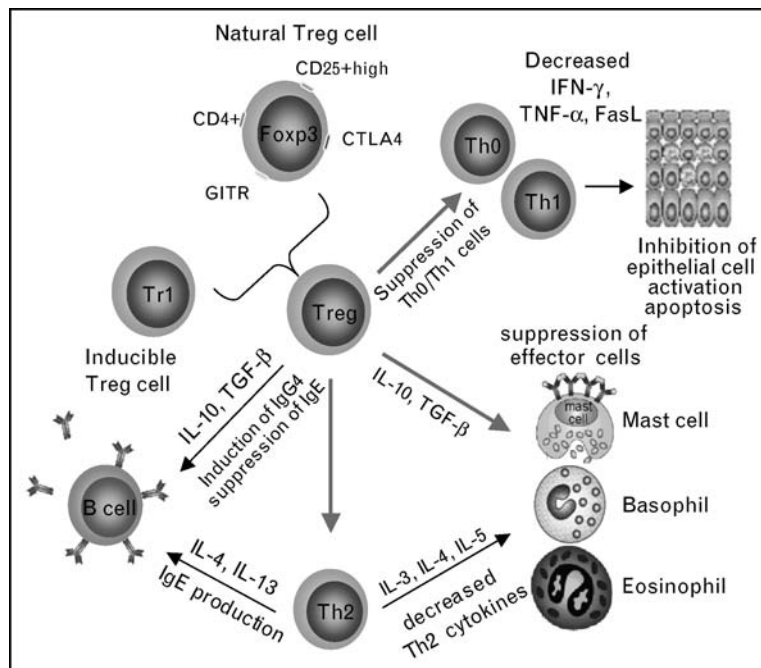
In another study [85], the ability of cutaneous resident dendritic cells to differentiate IL-22-producing cells was investigated. Indeed, both Langerhans cells and dermal dendritic cells significantly induced IL-22-producing CD4(+) and CD8(+) T cells from peripheral blood T cells and naive CD4(+) T cells in mixed leukocyte reactions. Surprisingly, the majority of IL-22-producing cells induced by Langerhans cells and dermal dendritic cells lacked the expression of IL-17, IFN- $\gamma$ , and IL-4. Thus, Langerhans cells and dermal dendritic cells preferentially induced helper T cells to produce only IL-22, possibly 'Th22' cells. Data indicate that cutaneous dendritic cells, especially Langerhans cells, may control the generation of distinct IL-22 producing Th22 cells infiltrating into the skin.

### Regulatory T cells

Subsets of Treg cells with distinct phenotypes and mechanisms of action include the naturally occurring,

thymus-selected CD4<sup>+</sup>CD25<sup>+</sup> Forkhead box protein 3 (FOXP3)<sup>+</sup> Treg cells and the inducible type 1 IL-10-secreting Treg cells (TR1 cells) [86]. Additionally, subsets of CD8<sup>+</sup> T cells,  $\gamma\delta$  T cells, dendritic cells, IL-10-producing B cells, NK cells and resident tissue cells, which might promote the generation of Treg cells, could contribute to suppressive and regulatory events [87]. Treg cells induce an abolished allergen-specific T-cell proliferation and suppressed Th1 and Th2 type cytokine secretion. In addition, Treg cells directly or indirectly suppress effector cells of allergic inflammation such as mast cells, basophils and eosinophils [88,89] (Fig. 2). Moreover, Treg cells can potently suppress IgE production, whereas simultaneously increasing production of noninflammatory isotypes IgG4 and IgA, respectively [88]. Several studies in humans have demonstrated that in healthy individuals, if an immune response to common environmental allergens is detectable, TR1 cells specific for such allergens represent the dominant subset [88,90–92]. Both healthy and allergic individuals display allergen-specific Th1, Th2 and TR1 cells that recognize the same T cell epitopes. Accordingly, depending on the predominant subset and the balance between Th2 and TR1 cells the individuals may develop allergy (Th2 predominance) or recovery (TR1 predominance). Similarly repeated exposure of nonallergic healthy beekeepers to bee venom allergens during the beekeeping season via skin represents a valuable model to ascertain mechanisms of T-cell tolerance induction. After multiple bee stings, venom antigen-specific Th1 and Th2 cells show clonal switch toward IL-10-secreting TR1 cells and impair capacity of allergen-specific T cells to proliferate and produce Th1 and Th2 cytokines. This regulation continues as long as venom exposure persists reaching initial levels within 2–3 months after bee stings [91].

The immune regulatory role of T cell-derived IL-10 in allergic disease has been extensively studied. IL-10-treated dendritic cells are potent suppressors of the development of AHR, inflammation, and Th2 cytokine production; these regulatory functions are at least in part through the induction of endogenous production of IL-10 [93]. IL-10 inhibits CD28 and ICOS costimulations of T cells via src homology 2 domain-containing protein tyrosine phosphatase (SHP)-1 [94]. Accordingly, spleen cells from SHP-1-deficient mice showed increased proliferation with CD28 and ICOS stimulation in comparison with wild-type mice. In conclusion, the rapid inhibition of the CD2, CD28 or ICOS costimulatory pathways by SHP-1 represents a novel mechanism for direct T-cell suppression by IL-10 [94]. Immunohistochemical analyses of lesional skin biopsies of atopic dermatitis patients revealed the presence of IL-10-secreting Tr1 cells, but not FoxP3<sup>+</sup> CD4<sup>+</sup>CD25<sup>+</sup> T cells [95]. Devoid of functional Treg cells in acute infiltrates in atopic dermatitis skin lesions suggest an imbalance in T-cell regulation [95].

**Figure 2** The role of T regulatory cells and allergic diseases

Treg cells have immunosuppressive functions and cytokine profiles distinct from that of either Th1 or Th2 cells. Regulatory T cells are classified as naturally occurring and inducible Treg cells. Treg cell response is characterized by an abolished allergen-specific T cell proliferation and the suppressed secretion of Th1 and Th2 type cytokines. Treg cells are able to inhibit the development of allergen specific Th2 and Th1 cell responses and therefore play an important role in healthy immune response to allergens. Treg cells potentially suppress IgE production and directly or indirectly suppress the activity of effector cells of allergic inflammation, such as eosinophils, basophils and mast cells. In patients with atopic dermatitis, there is an increased pool of circulating regulatory T cells. Skin biopsies atopic dermatitis patients also revealed overexpression of IL-10 and TGF- $\beta$ , but not CD4<sup>+</sup>CD25<sup>+</sup>.

In addition to IL-10, TGF- $\beta$  is a key cytokine in immune tolerance. It was demonstrated that orally administered TGF- $\beta$ , such as TGF- $\beta$  in human milk, retains and exerts its activity in the intestinal mucosa and can induce immune tolerance to dietary antigens. BALB/c mice treated orally with OVA and TGF- $\beta$  showed augmented reduction of OVA-specific IgE and IgG1 antibodies, T-cell reactivity, and immediate-type skin reactions when compared with the mice treated orally with OVA alone [96]. The data suggest that oral administration of TGF- $\beta$  might become a potential strategy to prevent allergic diseases, such as food allergy. The molecular mechanism of induction of FOXP3 in human Treg cells has been a long lasting question. Transforming growth factor- $\beta$  (TGF- $\beta$ ) induces the expression of the Runt-related transcription factors RUNX1 and RUNX3 in CD4<sup>+</sup> T cells [97<sup>••</sup>]. This induction seems to be a prerequisite for the binding of RUNX1 and RUNX3 to FOXP3 promoter. Inactivation of the gene encoding RUNX by small interfering RNA (siRNA)-mediated suppression of RUNX1 and RUNX3 in human T cells resulted in reduced expression of Foxp3 demonstrating Runx transcription factors as a molecular link in TGF- $\beta$ -induced Foxp3 expression in iT reg cell differentiation and function.

## Conclusion

Understanding the mechanisms enrolled in the development of tissue specific allergic diseases are essential to develop strategies for treatment and prevention. Skin and mucosal epithelial cell organization shows a significant difference, which is decisive in the initiation of early stages of allergic infiltration and maintenance of chronicity. Different capture and recognition of antigens take place in different allergic tissues due to tissue specific antigen-presenting cells with highly distinctive features acting for introduction to the immune effector cells, especially to T lymphocytes. Recent developments in T-cell subsets, particularly the extension of the knowledge on reciprocal-regulation and counter-balance between Th1 and Th2 cells to Th9, Th17, Th22 and Treg cells has increased our knowledge in mechanisms of immune regulation. Differences of chemokines and organ-selective migration of the inflammatory cells is another decisive factor for selection of tissues. In addition, frequency of mast cells, proinflammatory macrophages, propensity of subepithelial fibrocytes are factors that may contribute but still remain to be elucidated.

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## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 512).

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